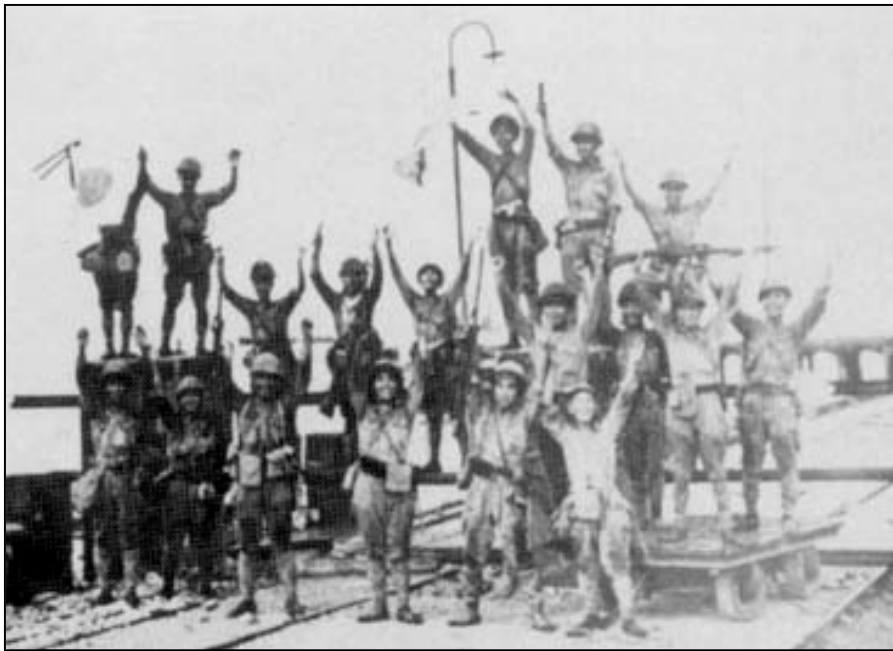


# **DoD Experience with Malaria and Antimalarials**

**Alan J. Magill  
COL / MC  
Science Director  
Walter Reed Army  
Institute of Research**

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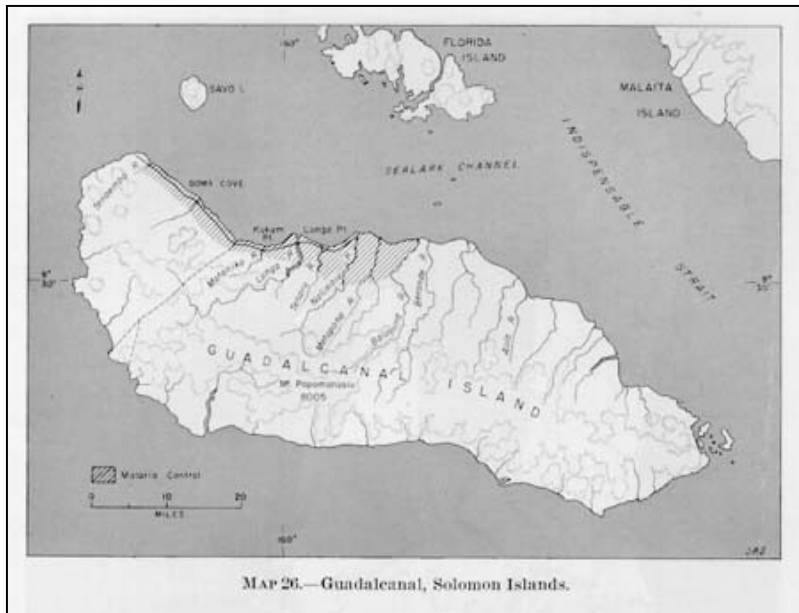
# World War II



**The Japanese 2d Division celebrates landing at Merak, Java, 1 March 1942!**

- **Japanese invasion of Java in Mar 1942**
- **Loss of quinine from Dutch East India**
- **Requires massive synthetic drug discovery program**

# World War II - Guadalcanal



**Marines land Aug 1942.  
1,781 malaria cases per 1,000 on Guadalcanal,  
in November 1943**

# World War II - Advances



**Chemoprophylaxis with Atabrine  
introduced in late 1943**

- **"Doctor, this will be a long war if for every division I have facing the enemy I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease!"**
  - **Statement to Dr. Paul Russell from Gen. Douglas MacArthur, May 1943**

# **World War II - Command Discipline**

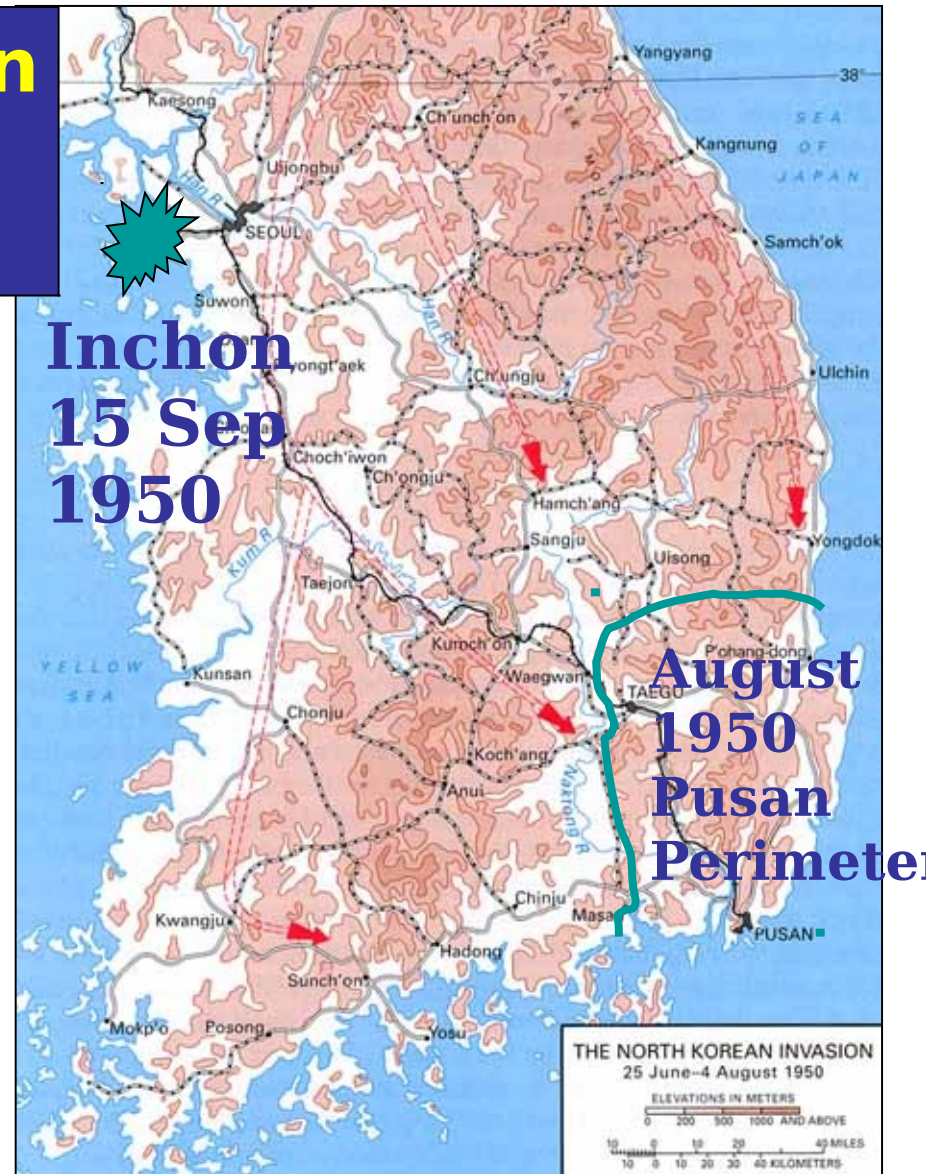
- **"You doctors think you can prevent malaria, but you can't. I can and I'm going to."**
- **"When for the first time in history a combatant officer was considered unfit to command a unit on the grounds that he had allowed his men to become ineffective through disease, a new day in military medicine dawned. The clouds of forgetfulness must not be allowed to overshadow the brightness of that day."**
  - **Sir Neil Cantlie, Director General of British Army Medical Services**

# Command Responsibility

- In World War II, LTG Sir William Slim stopped the longest, most humiliating retreat in the history of the British Army. When he assumed command in Burma in April 1942, the health of his troops was dismal. For each wounded man evacuated, 120 were evacuated with an illness. The malaria rate was 84 percent per year of total troop strength, even higher among the forward troops. In his memoirs, he describes his course of action:
- “... A simple calculation showed me that at this rate my army would have melted away. Indeed it was doing so before my eyes.”
- “Good doctors are of no use without good discipline. More than half the battle against disease is not fought by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine (anti-malarial chemoprophylactic drug used in W.W.II) is taken...if mepacrine was not taken, I sacked the commander. I only had to sack three; by then the rest had got my meaning.”
- “Slowly, but with increasing rapidity, as all of us, commanders, doctors, regimental officers, staff officers, and NCOs united in the drive against sickness, results began to appear. On the chart that hung on my wall the curves of admissions to hospitals and malaria in forward units sank lower and lower, until in 1945 the sickness rate for the whole 14th Army was one per thousand per day.”

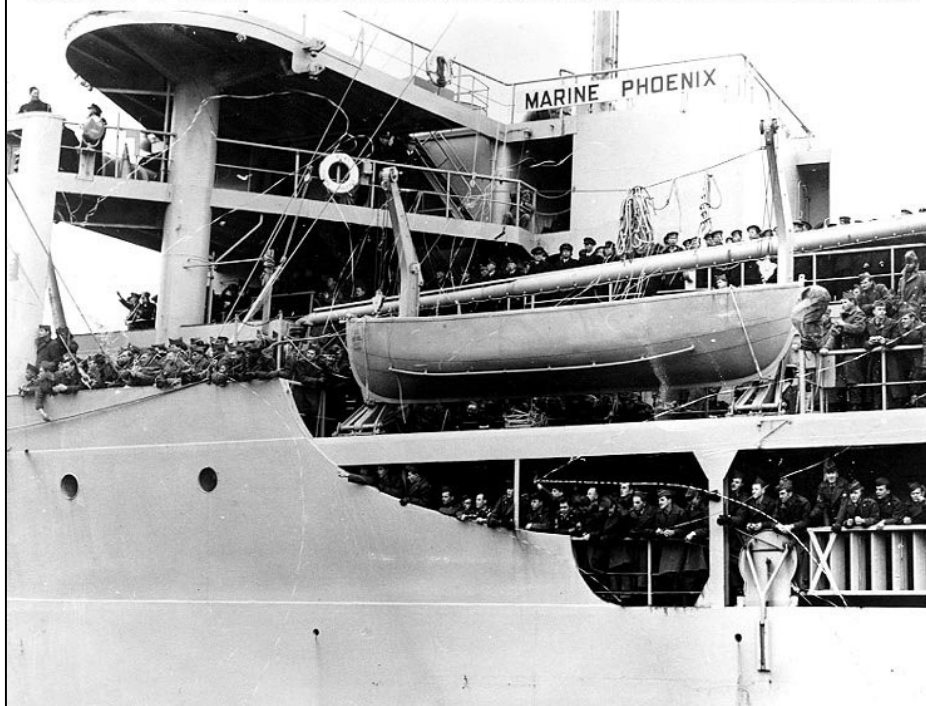


# North Korean Invasion Of South Korea, 25 Jun 1950



# Korean War - Advances

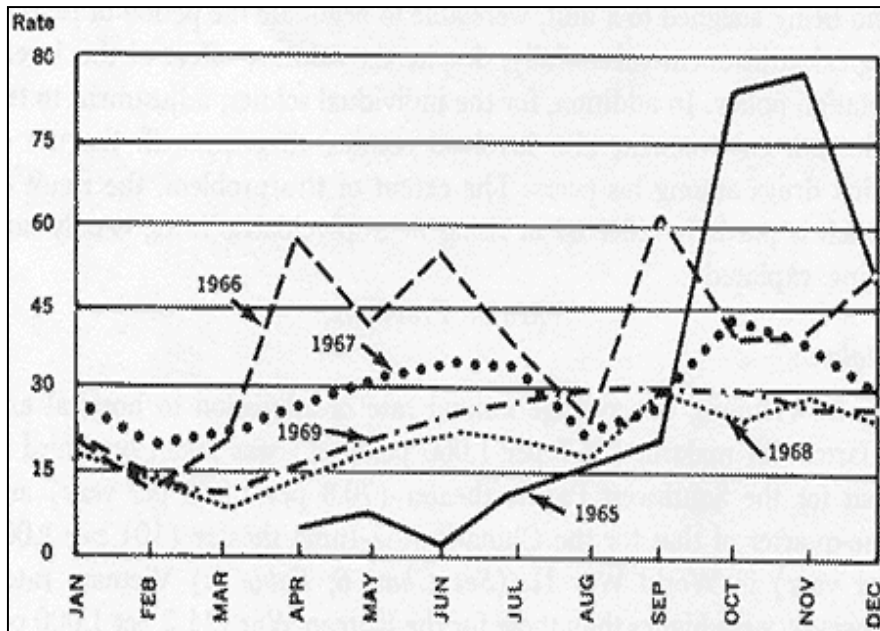
Photo # 80-G-438390 U.S. Soldiers and ROK Sailors aboard USNS Marine Phoenix, 1952



- **Use of primaquine for terminal prophylaxis and radical cure of relapsing *P. vivax* malaria**
- **Re-learn lessons of “command discipline”**



# Vietnam



- **78 deaths from malaria between 1965 and 1970**
- **Over a million man days lost**
- **1st experience with CQ-resistant *P. falciparum* malaria**
- **Mefloquine, developed by the Walter Reed Army Institute of Research, was first shown to be effective for prophylaxis and treatment of resistant *falciparum* malaria in the 1970s.**
- **MQ was FDA approved in 1989**

# Operation Restore Hope: Somalia, 1992-93



- 48 cases of malaria, 41 *P. falciparum*
- Difficult to enforce personal protection measures
- 5 breakthroughs on MQ
- Centralized diagnosis and care
- Canadian uses the “MQ defense”

# **FALCIPARUM MALARIA in US MARINES DEPLOYED TO LIBERIA, August 2003**



# Update: Recent Military Experiences

<b>Country</b>	<b>Forces</b>	<b>Outcomes</b>
<b>Liberia-2003</b>	<b>US Marines ~225 for 2 Weeks</b>	<b>80 Cases 5 Severe &amp; Complicated</b>
<b>Ivory Coast, Ghana, Senegal-2003</b>	<b>French ~4000 for 12 Months</b>	<b>707 cases (201 after Returning to France) 1 Severe &amp; Complicated</b>
<b>Nigeria-2001</b>	<b>US Special Forces 300 for Short Term Deployment</b>	<b>7 Cases 2 Severe and Complicated 1 Death</b>
<b>Sierra Leone-2000</b>	<b>British 4500</b>	<b>112 Cases 2 Severe &amp; Complicated</b>
<b>Angola-1995</b>	<b>Brazilian 439 for 6 Months</b>	<b>78 Cases 3 Deaths</b>

# **Importance of Malaria Prevention to the US Military**

- **Historical and current**
- **Prevention**
  - **Vector measures:**
    - **PPMs**
    - **Insecticides & area control measures**
    - **Anti-malarial chemoprophylaxis**
    - **Command discipline**



# **Anti-malarial chemoprophylaxis choices for US Military in 2004**

- **Chloroquine**
  - **Aralen® and generics**
- **Mefloquine**
  - **Lariam® and generics**
- **Doxycycline**
  - **Vibramycin® and generics**
- **Malarone® (atovaquone / proguanil)**

## **DoD Directive 6200.2 (Aug 2000): Use of Investigational New Drugs for Force Health Protection (FHP)**

- **Derived from Title 10: USC 1107, E.O 13139 & 21 CFR 50, 56, 312**
- **Anti-malarial chemoprophylaxis is a FHP activity**
- **Applies to FDA approved drugs used for unapproved indications (“off-label use”)**
- **Prevents military from using primaquine for primary prophylaxis**
- **Primaquine would be drug of choice for Afghanistan**

# **What is different about military use of anti-malarial chemoprophylaxis?**

- **Travel Medicine**

- Individual
- Travel
- Optimizing for the individual is the goal
- Encourage “adherence”
- One-one medical care
- “All comers”
- Special populations: children, pregnant, elderly, Disease co-morbidities
- Free to choose

- **Military Medicine**

- Unit
- The “mission”
- Optimizing for individual is difficult
- Require compliance
- Unit education
- “Pre-screened”
- Special populations: aviators, SOF, young, healthy, mostly male, no disease co-morbidities
- Required = Force Health Protection

# Atabrine in WWII: Perception vs. Reality



- **Effect of belief on behavior and illness**
- **Moderate but obvious side effects combined with rumor and folklore**
- **Persistent belief that Atabrine caused impotency and hepatitis**



## Were Vietnam malaria pills responsible for Vietnam vet illnesses?

**TOPIC:** Medical scientists believe that the anti-malaria pills taken by soldiers who served overseas between 1999 and 2002 might be responsible for behavioral problems, personality disorders and inability to control emotions and actions. Do you think that the malaria pills taken by Vietnam War personnel might be responsible for some of their similar ailments?

**Did you serve in Vietnam or the Indochina Theater during the Vietnam War era (1955 through 1975)?**

☐ Yes ☐ No

**Did you take the orange malaria tablets prescribed for weekly intake?**

☐ Yes ☐ No

**Do you belief or suspect that the anti-malaria pills you and other GI's took might be responsible for some of disorders Indochina Theater vets suffer from?**

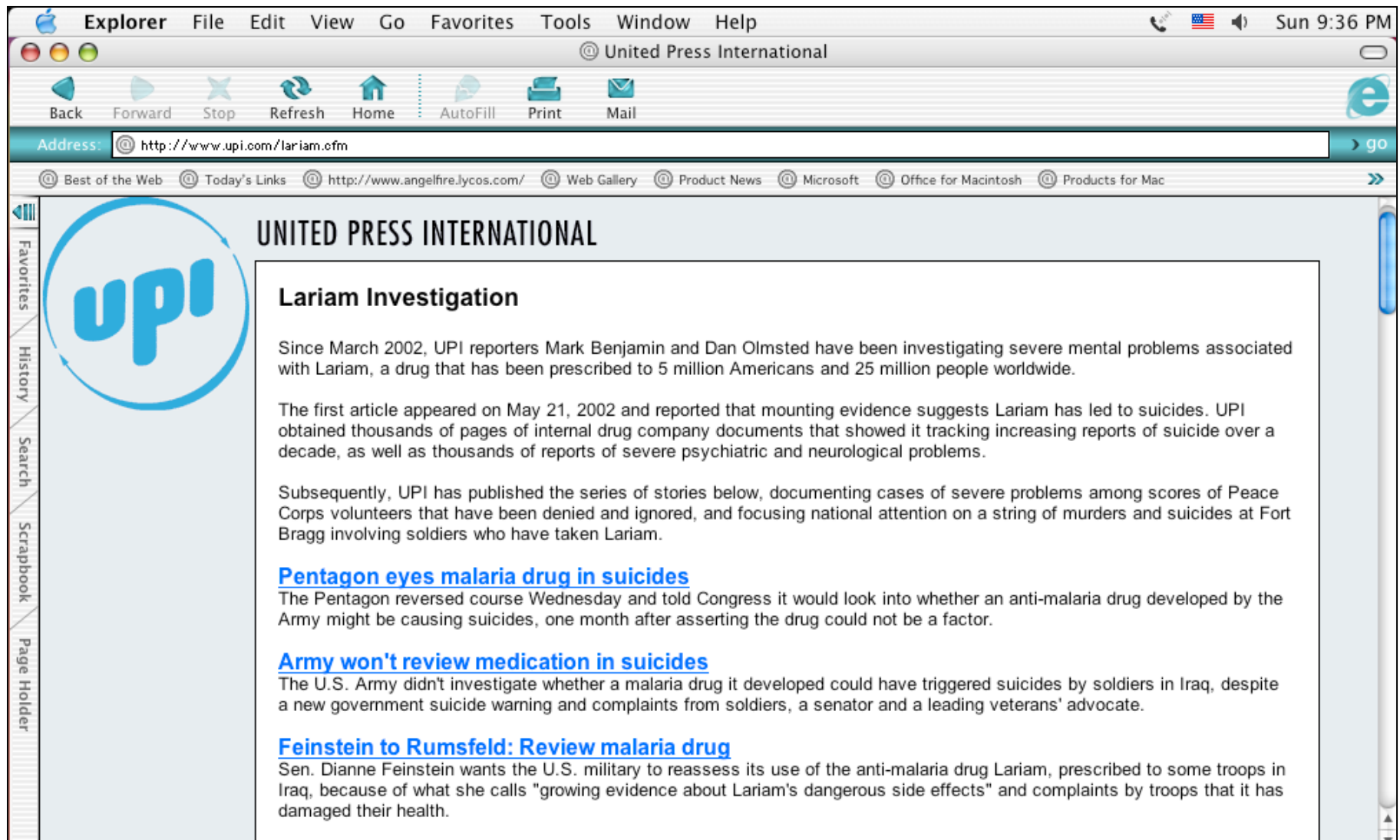
☐ Yes ☐ No

**Which branch did you serve?**

☐ Army ☐ Navy ☐ Marine ☐ Air Force ☐ Coast Guard ☐ Merchant Marine

<http://home.pacbell.net/veterans/xmalaria.ht>





**Series of press reports from Mark Benjamin & Dan  
from UPI beginning Mar 2002: <http://www.upi.com>**

12 April 2  
004

Mefloquine Adverse Event  
Study Design Meeting

19

# **Neuropsychiatric Adverse Events and Anti-Malarial Drugs**

- **Quinacrine (Atabrine & Mepacrine)**
- **Chloroquine (Aralen)**
- **Mefloquine (Lariam)**

# Operational Medicine

- **Thousands of deployed troops**
- **Variable knowledge of drug adverse events by docs and troops**
- **Difficult to “follow-up”**
- **Poor record keeping**
- **Disease reporting is incomplete, inaccurate, or not done**
- **Not possible to do research**

# **How and who decides anti-malarial chemoprophylaxis policy**

- **Preventive Medicine function**
- **OTSG / CHPPM / SMEs**
- **Unified Combatant Commands**
  - **Command surgeons and staff**
- **Task force and area commands**
- **Subordinate commanders policy modifications**
- **Army / Navy / Air Force**

# Primaquine: the Pacific Crossing, Dec 1951 - Dec 1953

Number Returning	Doses of PQ
332,925	14
21,499	13
24,932	12
21,493	11
9,348	10
5,143	<10
2,777	0
<b>Total = 418,117</b>	<b>&gt; 5.5 million</b>

- Minimal medical supervision
- No pre-testing for G6PDd
- Minimal toxicity
  - 20 d/c sea sickness
  - 2 d/c methemoglobinemia
  - 2 d/c “allergy”
  - 1 d/c urticaria
  - 1 d/c hemolytic anemia
- Archambeault CP. Mass antimalarial therapy in veterans returning from Korea. 1954. JAMA. 154(17); 1411



# **Why is MQ important to the military?**

- **MQ is the only weekly drug we have**
  - **Much easier to insure compliance**
  - **Not likely to get another weekly drug soon**
- **Very efficacious world-wide**
- **Military personnel will die of malaria if MQ not available**

# TO "LARIAM" OR NOT TO "LARIAM"

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